REMARKS

The following is a response to the Office Action mailed November 2, 2004, which the Examiner has made Final, and the Advisory Action mailed March 2, 2005.

Claims 1 to 4, 7 to 14, 18 to 22, and 24 to 26 are pending. Claims 1, 20 and 25 have been amended. Claims 28-31 have been added. Claims 5-6, 15-17, 23 and 27 were previously canceled.

Amendment to the claims is fully supported by the specification and claims as filed and therefore do not add new matter nor raise new issues.

Accordingly, entry of the amendment and withdrawal of the rejections is respectfully requested.

I. Rejection of claims under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-4, 7-14, 18-22 and 24-26 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the enablement requirement for the reasons as set forth in the Office Action mailed March 24, 2004. Applicants respectfully traverse this rejection.

According to Office Action mailed March 24, 2004, the specification does not provide evidence that any of the nucleic acids of the claims are mutated at a sufficiently early in the development of any type of cancer so as to be detectable prior to histological changes in the regions external or marginal to the neoplastic (or tumor) regions; and that the detection of such nucleic acids would be undue experimentation to one of ordinary skill in the art. Further, according to the same Office Action, the specification, absent *actual* evidence that a particular mutation or mutation in a particular nucleic acid occur sufficiently early in development of cancer so as to be detectable prior to histological changes in lymph nodes and /or surgical margins, one skilled in the art would not expect to be able to accomplish such detection.

Briefly, the problem solved by the claimed invention is the previous inability of others to determine and detect whether a tumor has been completely eradicated by a treatment (see, for example, page 3, lines 5-19). That is, whether histological and morphologically normal tissues as determined by microscopic examination harbor genes associated with the alleged eradicated tumor. The above claimed invention solves this problem by providing a method (e.g., PCR amplification) for detecting a mutant (or neoplastic) nucleic acids (e.g., APC, DCC, NF1, NF2, RET, VHL and WT-1), in tissue specimens that are "external" to the primary neoplasm, or tumor. These "external" tissue specimens do not exhibit characteristics indicative of neoplastic pathology even by microscopic analysis. As such, the application as filed sufficiently describes one of ordinary skill in the art to use the invention.

Examples 1-4 describe detection of neoplastic genes in neoplasms (tumors) as well as tumor margins. Typically when a tumor is surgically removed (e.g., tumor resection) the entire tumor is excised from the surrounding normal tissue margin. A "standard technique for assessing the spread of a tumor is surgical resection of a primary tumor followed by careful review using light microscopy of surgical margins and other tissue, including lymph nodes (page 3, lines 9-11)." Yet, "[d]espite many years of research and billions of dollars in expenditures the long term survival of patients with malignancies remains disappointedly low, even where no tumor cells were detected in the tumor margins or more distant tissues (page 3, lines 22)." Hence, the "standard technique" described in the art is not a "precise technique capable of determining the spread the disease at an earlier stage...page 3, lines 25-26)."

"The principal advantage of the method of this invention is that the PCR method of amplification can be used to detect one cancer cell in ten thousand cells in tissue margins of tumors. This high sensitivity is far superior to results obtained by the prior art methods of histologic examination. Moreover, this invention provides the diagnostician with an opportunity to screen tissue from patients determined to be at risk of developing tumors at an early stage before discernible tumors actually ...(page 73, lines 6-14)." The present invention also describes the tissue margins as the "negative" surgical margins (page 65, line 16), implying that because

the tumor has been surgically removed or resected, the intact tissue left behind is normal or "negative." Thus, the claimed invention provides a "more accurate indication of the *extent* of tumor metastases into adjacent and regional tissues (emphasis added, page 3, lines 27-28)."

Contrary to what the Office Action states, the claimed invention does *not* depend on any *actual* evidence that a particular mutation or mutation in a particular nucleic acid occur sufficiently *early* in development of cancer so as to be detectable prior to histological changes. The methods of the claimed invention are independent of when the neoplastic genes are expressed. The claimed invention determines whether and to what *extent,* the tissue and cells having neoplastic genes have been successfully eradicated or excised; and PCR amplification increases the level of sensitivity which this detection can be determined. In short, the claimed invention has less to do with whether certain neoplastic genes are expressed "early" in the development of a tumor as it does to whether any neoplastic gene exists in what would otherwise be normal and healthy tissue.

Additionally, the Advisory Action mailed March 2, 2005 states that although Applicants describe methods of detecting neoplastic genes in neoplasms (tumors) as well as in histologically normal tissue, that at least claims 1 and 20 as such did not recite the same. Applicants submit that amendment of independent claims 1 and 20 unambiguously recite that which Applicants believe to be the subject matter of the invention. That is, the claimed invention recites a method for detecting and extracting a neoplastic gene from a neoplasm as well as from tumor margin tissue specimens which do not exhibit *microscopic* characteristics of a neoplasm. New claims 28-32 are also drawn to methods wherein the specimen (e.g., surgical margin, specimen external to the primary neoplasm, and lymph node) do not exhibit *microscopic* characteristics of a neoplasm.

Therefore, Applicants submit that the application as filed, fully, clearly and concisely describes the claimed invention in such a way as to enable one skilled in the art to use the invention.

Accordingly, withdrawal of the rejections of the claims under 35 U.S.C. § 112, first paragraph is respectfully requested.

Conclusion

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 07-1896.

Respectfully submitted,

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